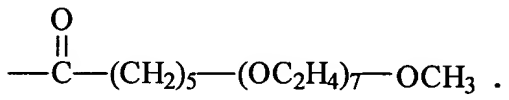
70. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

a10

71. (New) The mixture according to claim 16, wherein at least one of the oligomers is covalently coupled to Lys^{B29} of the human insulin and has the formula:



Please cancel claims 4-6, 12-15, 31-39, 42-45, 49, 51, and 53-67 without prejudice or disclaimer.

Remarks

Applicants appreciate the thoughtful and complete examination of the present application as evidenced by the Office Action mailed February 24, 2003 (the Action).

1. Status of Claims

The Examiner has allowed claims 40 and 41 are allowed, and has indicated that claims 7, 16, 49, and 51 contain allowable subject matter and would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 4-6, 12-15, 31-39, 42-45, 49, 51, and 53-67 were rejected.

The entry of this Amendment results in the cancellation of the rejected claims 4-6, 12-15, 31-39, 42-45, 49, 51, and 53-67, and the addition of new claims 68-71. Claims 1-3, 7-11, 16-30, 40-41, 46-48, 50, 52, and 68-71 are now pending in the application.

2. Amendments to Place Application in Condition for Allowance

Pursuant to the telephonic interviews conducted with Examiner Russel on March 14, 2003 and March 31, 2003, Applicants have amended claims 1, 7, 17, 10, 16-22, 25-28, 30, 46, 50, and 52 in a manner consistent with the proposed amendments discussed with the Examiner on March 31, 2003 during which the Examiner indicated that the proposed amendments will overcome the rejections of the current Action. *See* Interview Summary dated April 1, 2003, page 3. Support for the amendments to the claims can be found in the originally filed claims and/or the specification.

Claims 7, 17, and 22 have been specifically amended to address the antecedent basis issues raised by the Examiner during the March 31, 2003 telephonic interview and reiterated in the Interview Summary dated April 1, 2003.

Claim 52 has been specifically amended in order to address the issue regarding capitalization raised by the Examiner during the March 31, 2003 telephonic interview and reiterated in the Interview Summary dated April 1, 2003.

Applicants have added new claims 68-71. Support for new claims 68-71 can be found in the originally filed claims and/or the specification. No new matter is added by these amendments or new claims and Applicants respectfully request their entry into the present application.

3. Supplemental Information Disclosure Statement

Applicants submit concurrently herewith a Supplemental Information Disclosure Statement which includes an abstract entitled "Stability and Physical Characteristics of Orally Active Amphiphilic Human Insulin Analog, Methoxy (Polyethylene Glycol) Hexanoyl Human Recombinant Insulin (HIM2)" (the abstract). It is Applicants' understanding that, as indicated by the title page submitted with the abstract, the abstract first appeared in the Program Book of The 27th International Symposium on Controlled Release of Bioactive Materials and the Third Consumer and Diversified Products Conference that was held July 7-13, 2000. *See* Appendix,

Tab 1. Consequently, the abstract cannot be considered prior art to the application under 35 U.S.C. § 102.

4. In re Katz Declaration

Applicants also submit concurrently herewith a Declaration of Balasingam Radhakrishnan, Ph.D. under 37 C.F.R. § 1.131 and *In re Katz.*[1] *See* Appendix, Tab 2.

5. Obviousness-Based Double Patenting Rejection Obviated

As noted during the telephonic interview with the Examiner on March 31, 2003, copending Application No. 09/873,797 has not issued and none of claims 1-103 have been allowed. Accordingly, Applicants respectfully request that the provisional rejection of claims 1-6, 8-15, 17-39, 42-48, 50, and 52-67 be withdrawn.

Furthermore, in Applicants' voice mail message to the Examiner recorded on April 9, 2003, Applicants filed a Request for Continued Examination (RCE) and a Supplemental Information Disclosure Statement in U.S. Patent Application Serial No. 09/873,731 on April 10, 2003 (Copy of RCE as filed is enclosed.), thereby obviating the need for filing a Terminal Disclaimer with this response.

However, Applicants will provide a Terminal Disclaimer if it is determined to be necessary upon allowance of the relevant claims. Accordingly, Applicants respectfully request that the provisional rejection of claims 59-67 be withdrawn.

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[1] 687 F.2d 450, 215 U.S.P.Q. 14 (C.C.P.A. 1982).

Conclusion

In view of the amendments to the claims, Applicants respectfully request withdrawal of the claim rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103(a), the provisional rejections under the judicially created doctrine of obviousness-type double patenting, and the claim objections as set forth in the Action.

With the concerns of the Examiner addressed in full, Applicants respectfully request reconsideration of this application and the issuance of a Notice of Allowance forthwith. The Examiner is encouraged to direct any questions regarding the foregoing to the undersigned, who may be reached at (919) 854-1400.

A check in the amount of $180.00 for submission of a Supplemental Information Disclosure Statement under 37 C.F.R. § 1.97(c) is included herewith. No additional fee is believed due. However, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 50-0220.

Respectfully submitted,

Mary L. Miller
Registration No. 39,303

20792
PATENT TRADEMARK OFFICE

Certificate of Mailing under 37 CFR 1.8
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on April 23, 2003.

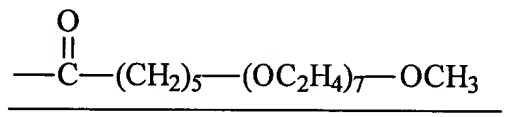
Monica L. Croom

Version With Markings To Show Changes Made

In the claims:

Please amend claim 1 as follows.

1. (Amended) A mixture of conjugates, each comprising **[an]** a human insulin drug coupled to an oligomer **[that comprises a polyethylene glycol moiety,]** having a formula:



wherein the mixture has a dispersity coefficient (DC) greater than 10,000, where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

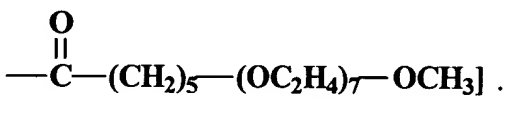
n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

Please amend claim 7 as follows.

7. (Amended) The mixture according to Claim 1, wherein the **[insulin drug is human insulin and the]**oligomer is covalently coupled to Lys^{B29} of the human insulin drug **[and has the formula:**



Please amend claim 10 as follows.

10. (Amended) The mixture according to Claim 1, wherein the **[mixture]** human insulin-drug oligomer has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

Please amend claim 16 as follows.

16. (Amended) A mixture of conjugates, each comprising insulin coupled to an oligomer that comprises a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000, where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule; and

wherein the conjugate comprises a first oligomer and a second oligomer; and

[The mixture according to Claim 15]

wherein the first oligomer is covalently coupled at Lys^{B29} of the insulin and the second oligomer is covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.

Please amend claim 17 as follows.

17. (Amended) The mixture according to Claim 1, wherein the human insulin drug is covalently coupled to the oligomer.

Please amend claim 18 as follows.

18. (Amended) The mixture according to Claim **[1]** 16, wherein the insulin **[drug]** is covalently coupled to at least one of the **[oligomer]** oligomers by a hydrolyzable bond.

Please amend claim 19 as follows.

19. (Amended) The mixture according to Claim **[1]** 16, wherein the insulin is covalently coupled to the polyethylene glycol moiety of at least one of the **[oligomer]** oligomers.

Please amend claim 20 as follows.

20. (Amended) The mixture according to Claim **[19]** 16, wherein at least one of the **[oligomer]** oligomers **[further]** comprises a lipophilic moiety covalently coupled to the polyethylene glycol moiety.

Please amend claim 21 as follows.

21. (Amended) The mixture according to Claim **[1]** 16, wherein at least one of the **[oligomer]** oligomers **[further]** comprises a lipophilic moiety.

Please amend claim 22 as follows.

22. The mixture according to Claim 21, wherein the insulin **[drug]** is covalently coupled to the lipophilic moiety.

Please amend claim 25 as follows.

25. (Amended) The mixture according to Claim **[24]** 16, wherein the first and the second oligomers are the same.

Please amend claim 26 as follows.

26. (Amended) The mixture according to Claim [1] 16, wherein at least one of the oligomers **[oligomer]** comprises a first polyethylene glycol moiety covalently coupled to the

insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

Please amend claim 27 as follows.

27. (Amended) The mixture according to Claim 26, wherein the oligomer(s) comprising a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond further **[comprises]** comprise a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

Please amend claim 28 as follows.

28. (Amended) The mixture according to Claim **[1]** 16, wherein each of the conjugates is **[are each]** amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

Please amend claim 30 as follows.

30. (Amended) A method of treating insulin deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of the composition of claim 1 **[a mixture of conjugates each comprising an insulin drug coupled to an oligomer comprising a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where**

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

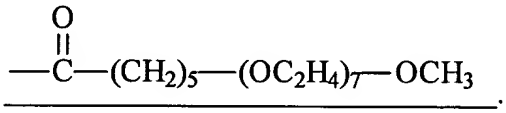
N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule;]

to the subject to treat the insulin deficiency.

Please amend claim 46 as follows.

46. (Amended) A mixture of conjugates, each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, wherein the insulin drug is human insulin, and the oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:



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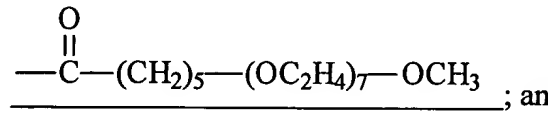
Please amend claim 50 as follows.

50. (Amended) A mixture of conjugates **[in which each conjugate: comprises an insulin drug coupled to an oligomer; and has the same number of polyethylene glycol subunits]**, each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety,

wherein each polyethylene glycol moiety has the same number of polyethylene glycol subunits,

wherein each oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:

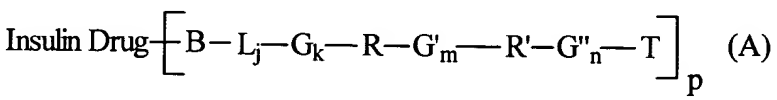


; and

wherein the mixture has a molecular weight distribution with a standard deviation of less than about 22 Daltons.

Please amend claim 52 as follows.

52. (Amended) A mixture of conjugates in which each conjugate is the same and has the formula:



(A)

wherein:

B is carbonyl;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is C_5 alkylene and R' is polyethylene glycol having 7 polyethylene glycol subunits **[R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety]**;

T is methoxy;

j**[, k, m and n are individually]** is 0 or 1;

k, m and n are 0; and

p is an integer from 1 to the number of nucleophilic residues on the insulin drug.